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| 10/596,528   | 05/01/2008  | Venkata P. Palle     | RLL-419US                       | 7589                        |
| 26815  | 7590        | 12/02/2009           |                                 |                             |
| Ranbaxy Inc.<br>Intellectual Property Department<br>600 College Road East<br>PRINCETON, NJ 08540 |             |                      | EXAMINER<br>BERCH, MARK L       |                             |
|  |             |                      | ART UNIT<br>1624                | PAPER NUMBER                |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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|                              |                                      |                                     |  |
|------------------------------|--------------------------------------|-------------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/596,528 | <b>Applicant(s)</b><br>PALLE ET AL. |  |
|                              | <b>Examiner</b><br>Mark L. Berch     | <b>Art Unit</b><br>1624             |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. ____.                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>03/04/2008</u> .  | 6) <input type="checkbox"/> Other: ____.                          |

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The definition of alkyl on page 17 is so broad that it is unclear what applicants actually intend, since it can be things which do not remotely look like alkyl in the normal meaning of the term. Lines 22-23 permit an interruption by e.g. O, so that alkyl=methyl can be interrupted by O and become methoxy. The definition includes substituted versions thereof, so that for example, methyl can be substituted by oxo and OH (line 7), and therefore become COOH, carboxy. Or it could be substituted by oxo and phenyl to be the C(O)Ph, i.e. benzoyl group. These of could can be interrupted by O and this includes the OC(O)OH (bicarbonate) group or OC(O)Ph, benzoyloxy groups. Similarly, groups such as CONH<sub>2</sub>, and other things bearing no resemblance to alkyl are covered.
2. The definition of cycloalkyl includes unsaturated cyclic hydrocarbon, which would include the phenyl ring. Is that intended?

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3. The definition of acyl is unclear. The problem is that applicants have two definitions of page 22, one at line 20 and one at line 26. These are not the same. For example, the former would include COOH; the latter would not.
4. Page 22, lines 16-17 has the following: "The term "heteroarylalkyl" refers to alkyl-heteroaryl group wherein the alkyl and heteroaryl are the same as defined earlier." This does not make sense, because the positions of the heteroaryl and the alkyl have been switched. In heteroarylalkyl, the bonding of the groups is via the alkyl; in to alkyl-heteroaryl, it is via the ring. Hence, things are unclear. The same problem occurs in the following two lines.
5. In a similar problem, page 20, lines 13-15 is self-contradictory. It states: "The term "alkaryl" or "aralkyl," unless otherwise specified, refers to  $(CH_2)_p$ aryl, wherein p can be an integer in the range of 1-6 and aryl is as defined below. Examples of alkaryl include benzyl, ethylphenyl and the like." The definition says that both terms mean the same thing, i.e. to  $(CH_2)_p$ aryl, which has the group bonded via the alkylene chain. Benzyl meets that definition, but "ethylphenyl" does not, since ethylphenyl is bound via the phenyl, not the alkyl piece.
6. There are two description for R2/R3 in the claims; these need to be joined by "or".
7. The term "thioalkoxy" is indefinite. This could be alkylthio, or it could be mercaptoalkyl. For whichever choice is selected, applicants must show that one skilled in the art could have figured out that this choice, and not another, was surely intended.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds themselves, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates are not enabled. The numerous examples presented all failed to produce a solvate. The evidence of the specification is thus clear: These compounds do not possess the property of forming solvates; there is no evidence that such compounds even exist. Thus, this is a circumstance where the “specification is evidence of its own inadequacy” (*In re Rainer*, 377 F.2d 1006, 1012, 153 USPQ 802, 807). These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F)

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The amount of direction provided by the inventor: (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the wide scope of the 6 primary variables, trillions of compounds are covered.

(b) Scope of the diseases covered.

I. The scope of treating inflammation generally is extraordinarily broad. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. It is one of the most pervasive of all body processes. Inflammation is a very general term which encompasses a huge variety of specific processes.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Mechanistically, chronic inflammation

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encompasses a broad spectrum of immunologic processes, including antibody formation, antibody-dependent cell-mediated cytotoxicity, and cell-mediated immunity (delayed-type hypersensitivity). Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Cystitis is any inflammation of the bladder, often caused by bacteria. Two ordinary types are eosinophilic and tuberculous cystitis. Interstitial cystitis (IC) is a particularly severe form, an inflammation of the bladder wall which may include Glomerulations. The origins and mechanism are largely unknown, and it isn't even clear whether there is just one form of the disease or several. There is no actual pharmaceutical treatment for the disease itself, although a few drugs can give some relief of symptoms, specifically Elmiron and DMSO.

Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

There is also a wide assortment of forms of conjunctivitis, including seasonal allergic conjunctivitis, perennial allergic conjunctivitis, giant papillary conjunctivitis (GPC) (a chronic yet poorly condition associated with contact lens wear), Vernal keratoconjunctivitis and atopic keratoconjunctivitis. In addition to types of allergic conjunctivitis there is also bacterial conjunctivitis (e.g. from *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*) and viral conjunctivitis (e.g. from gonorrhea, herpes simplex, chlamydia, adenoviruses or enteroviruses) Parasitic conjunctivitis (e.g. from *Onchocerca volvulus*, *Loa loa*, *Wuchereria bancrofti* or *Trichinella spiralis*), fungal conjunctivitis (e.g. from *Candida albicans* or *Sporothrix schenckii*), Phlyctenular Conjunctivitis, Inclusion Conjunctivitis, immunologic conjunctivitis, irritant conjunctivitis (e.g. from burns, chlorine or air pollutants ), Radiation conjunctivitis, and assorted forms of neonatal conjunctivitis (which can be caused by e.g. a blocked tear duct).

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as *Salmonella*, *Staphylococcus*, *Streptococcus* (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

The term “arthritis” is used for any of the dozens of kinds of inflammation of the joints arising from a wide diversity of causes and mediators, many of which are unknown. It mostly commonly refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have “arthritis” in their



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name and involve inflammation of the joints. Rheumatoid arthritis is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, TNF-I and IFN-K. It is thus an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long term obesity, but often the cause is unknown, and the full mechanism has not been discovered. It is treated with NSAIDs and COX-2 inhibitors. Complicating matters further is that fibromyalgia is sometimes also intended to be included in the loose term "arthritis". There is also Psoriatic Arthritis (including DIP, and spondylitis) which is believed to be autoimmune in origin but is a separate disorder from RA. There are also an assortment of infectious arthritis, i.e. arthritis caused by bacteria, rickettsiae, mycoplasmas, viruses (or vaccinations given to prevent viral infections), fungi, or parasites. Included in this category are various types of septic arthritis and mycotic arthritis, and viral arthritis, such as rubella arthritis, Lyme arthritis (caused by a spirochete transmitted by a tick), Mumps arthritis, arboviral arthritis, syphilitic arthritis, parvovirus arthritis, tuberculous arthritis, Varicella arthritis, gonococcal arthritis, rubella arthritis, Reiter's syndrome (which includes a form of arthritis commonly arising from infection by *Chlamydia trachomatis*) etc. These assorted disorders can arise from quite varied sources. Thus, in addition to the above, CPDD,

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sometimes called pseudoosteoarthritis, or pseudogout, arises from Calcium Pyrophosphate Deposition. It is treated with nonsteroidal anti-inflammatory drugs, corticosteroids and Colchicine. Menopausal arthritis is due to ovarian hormonal deficiency. Neuropathic arthritis (which comes in several forms, such as Charcot's disease) can arise from sources as diverse as Diabetes Mellitus, Steroid treatment, Leprosy, Chronic alcoholism, Heavy metal poisoning and Neoplastic peripheral neuropathy. Arthritis can also arise from injury to the supporting ligaments or other structures contained within or associated with the joint, a condition often called post-traumatic arthritis. Juvenile Dermatomyositis (JDMS) is an inflammatory disease of unknown cause that affects the skin, muscle and the gastrointestinal tract. Polymyalgia Rheumatica (PMR) causes severe stiffness, aching and pain in the neck, shoulders, upper arms, lower back, hips or thighs. Polymyositis is due to inflammation of skeletal muscle, resulting in weakness.

Sinusitis is the inflammation of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma to the nose, and foreign objects that are stuck in the nose. Bacteria, notably *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* grown in the trapped secretions. In most cases it requires no treatment, but antibiotics may be given, along with acetaminophen for pain and nosedrops, for relief of symptoms.

Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate) and tonsillitis is of the tonsils. These are caused by a variety of

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viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. *Mycoplasma pneumoniae*), and bacteria (Group A Beta Hemolytic Streptococci (GABHS), *Streptococcus pyogenes*, *Neisseria Gonorrhea*, *Hemophilus Influenza* Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes.

Similarly, Osteomyelitis is the inflammation of bones, often caused by bacteria (most commonly *Staphylococcus Aureus*), and sometimes by fungi or viruses. Chronic Recurrent Multifocal Osteomyelitis (CRMO), a chronic inflammatory disease of unknown etiology, results in recurrent fever and the development of multiple inflammatory bone lesions.

Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza.

Lung inflammation can take many forms.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD

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typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Another category of inflammatory disorders of the lung is Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis), a term that includes more than 180 chronic lung disorders, which may be chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium -- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. An important group of the ILDs are the Idiopathic interstitial pneumonias including idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia, Respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia and lymphoid interstitial pneumonia. Other ILDs are bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis. The cause of interstitial lung disease is not known,

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however, a major contributing factor is thought to be inhaling environmental pollutants.

Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness.

Lung inflammation includes most Occupational Lung Diseases, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), aluminosis, anthracosis ("collier's lung", from the accumulation of carbon from inhaled smoke or coal dust in the lungs), chalicosis (stone-cutters' lung disease, due to inhaling stone dust), siderosis (occurring in iron workers, produced by the inhalation of particles of iron), tabacosis. Some of these are grouped together as hypersensitivity pneumonitis. These include Farmer's Lung arising from fungus spores from e.g. moldy hay, Bird-Breeder's Lung, arising from various bird proteins, Humidifier Lung, arising from bacteria fungi, and even amoebae found in mists, from standing water, Malt Worker's Lung from moldy barley, and many other forms.

There is also Radiation pneumonitis, a consequence of radiation therapy done to the chest, generally for lung or breast cancer.

Lung inflammation includes Pneumonia. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bacterial pneumonia is caused by various bacteria notably *Streptococcus pneumoniae*. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza). There is no clearly effective treatment for viral

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pneumonia. Pneumonia can also occur as a hypersensitivity, or allergic response, or from mycoplasmas, rickettsias (especially Q fever), and Chlamydia.

Eosinophilic pneumonia, also called eosinophilic pneumonitis includes Löffler's syndrome and similar pneumonias such as tropical eosinophilia. These do not have alveoli infected by bacteria, viruses, or fungi, but instead, the alveoli and often the airways do fill with eosinophils. Why the eosinophils accumulate in the lungs is not well understood, and it can be triggered by things as varied as penicillin, fungi and parasites. Chronic eosinophilic pneumonia (CEP, also called Carrington's eosinophilic pneumonitis) is a related but somewhat different syndrome, and can easily be life threatening.

There is also asthma, either of the allergic type (generally considered an immune disorder) as well as occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors).

Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment is purely supportive and may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation.

Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the

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result of an asthma attack, or it may be the cause of an asthma attack.) Acute bronchitis is usually a mild, and self-limiting condition, with complete healing and return to function. Most of the treatment is supportive of the symptoms, and may include analgesics, such as acetaminophen for fever and discomfort.

Another disease characterized by lung inflammation is Cystic fibrosis (CF), characterized by an abnormality in the glands that produce sweat and mucus. It is chronic, progressive, and is usually fatal. The basis for the problem with CF lies in an abnormal gene, which results in an atypical electrolyte transport system within the cells of the body. The abnormal transport system causes the cells in the respiratory system, especially the lungs, to absorb too much sodium and water. This causes the normal thin secretions in the lungs to become very thick and hard to remove. The high risk of infection in the respiratory system leads to damage in the lungs, and eventually death of the cells in the lungs. The etiology of chronic inflammation, however, remains unclear. The disorder itself is largely untreatable.

Acute (or Adult) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly, arising from damage to capillary endothelium and alveolar epithelium caused by leukotrienes, oxidants, platelet-activating factor, and/or proteases. ARDS is a devastating, often fatal, inflammatory lung condition that, unlike most lung disorders, usually occurs in conjunction with catastrophic systemic conditions, especially shock, sepsis, and nonpulmonary trauma. No specific pharmaceutical therapies currently exist for ARDS per se. Treatment primarily involves supportive care in an intensive care unit, including use of a mechanical ventilator and supplemental oxygen to help patients breathe, plus in some cases, treatment of the

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underlying disorder (typically, sepsis) which has triggered the ARDS. Acute Lung Injury is the same clinical disorder, differing only in having a lesser degree of hypoxemia.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Mucocutaneous lymph node syndrome (MLNS) or Kawasaki syndrome is a potentially fatal inflammatory disease that affects the heart, circulatory system, mucous membranes, skin, and immune system. Its cause is unknown.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is the inflammation of the meninges—the surrounding 3-layered membranes of the brain and spinal cord, and the fluid it is bathed in, (CSF). It can be caused by virtually any known infectious agent. Thus, if it is caused by



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*Haemophilus influenzae* or *Neisseria meningitis*, the antibiotic derivative rifampin would be used.

Myelitis is inflammation of the spinal cord.

Dactylitis is an inflammatory affection of the fingers.

Inclusion body myositis is an inflammatory slowly progressive proximal myopathy which may cause dysphagia and mild to moderate muscle wasting. Steroids and immunosuppression have generally been generally ineffective. Its pathogenesis is unknown, but ubiquitin, prion protein, and tau protein has been found in these inclusions.

Behçet's disease is a syndrome of unknown origin, but appears to be an autoimmune disorder. It is characterized primarily by inflammation of the blood vessels. Symptoms include a broad range of problems, which include mouth sores, genital sores, skin sores or lesions, meningoencephalitis, Uveitis, inflammation of the joints, thrombophlebitis, aneurysms, digestive tract ulceration (sometimes called Behçet's colitis)

Encephalitis is inflammation of the brain itself, often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Inflammation in the brain is a significant component of some important neurodegenerative conditions, including Alzheimer's Disease, AIDS dementia, Pick's Disease, Parkinson's Disease, and Huntington's Disease. The circumstances here are poorly understood because while there does not appear to be

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lympho-infiltrative processes, there is neuropathological evidence for immune activation. Thus, inflammation may be a disease-aggravating or even a disease-ameliorating factor in pathogenesis, or a non-contributory consequence of the injurious cascade of neurodegeneration and thus incidental.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending

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chemical agent, or the administration of antibiotics, when *Neisseria gonorrhoeae* is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially *Candida albicans*), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of *Mycobacterium paratuberculosis*. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics

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if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Proctitis is a form of inflammation of the rectum, and includes Antibiotic-Induced Proctitis, Gonorrheal Proctitis, Herpetic Proctitis, Ischemic Proctitis, Radiation Proctitis, Syphilitic Proctitis and idiopathic proctitis.

Pulmonary Sarcoidosis causes small lumps, or granulomas, which generally heal and disappear on their own. However, for those granulomas that do not heal, the tissue can remain inflamed and become scarred, or fibrotic. Pulmonary sarcoidosis can develop into pulmonary fibrosis. Bronchiectasis, a lung disease in which pockets form in the air tubes of the lung and become sites for infection, can also occur. Treatment may include the use of corticosteroids.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as *Candida albicans*, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to *Lactobacillus* capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and

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fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral medications, inhaled medications, immunotherapy, and surgery for some conditions. Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is a type of inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis,

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toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelmintic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine. Vogt-Koyanagi-Harada syndrome (Harada's disease) is an acute inflammatory, immune-mediated disorder that can cause choroidal neovascularization, severe chorioretinal atrophy, and secondary glaucoma.

River blindness arises from inflammation of the eye caused by larvae (microfilaria) of the nematode *Onchocerca volvulus*, although the *Wolbachia* bacteria may be involved as well.

Multifocal choroiditis and panuveitis (MCP) is a posterior chorioretinal inflammatory disease of unknown etiology

There are also other forms of choroiditis, inflammation of the middle coat (choroid) of the eyeball, as well as uveitis, which is inflammation of the parts of the eyes that make up the iris. Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from *Helicobacter pylori*. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee sting), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus *Propionibacterium acnes*, which populates the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened)

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because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obliterans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease; it is of unknown origin), tuberculous arteritis, endarteritis obliterans, and verminous mesenteric arteritis.



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Osgood-Schlatter disease is a common form of inflammation of the knee in active adolescents. It has no pharmaceutical treatment per se. Other inflammations of the knee include Sinding-Larsen-Johansson disease, Patellofemoral syndrome, and osteochondritis dissecans.

Adhesive capsulitis is a type of inflammation of the shoulder. Its origin is usually unknown.

There can be a generalized inflammatory response of the entire body. When it arises from a proven source of infection, it is called sepsis. When it does not, it is called systemic inflammatory response syndrome (SIRS). Both of these are characterized by extensive cytokine dysregulation.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It should be noted that determining that a disorder is an inflammatory one is sometimes not an easy manner. For example, it has taken decades of research to discover that the destruction of the central area of the retina, which is the hallmark of age-related macular degeneration, actually arises out of an inflammatory process, involving the Complement Pathway. This only became well established in 2005. It is entirely possible that a majority of disorders presented considered idiopathic --- including many untreatable disorders --- are in fact inflammatory disorders.

It must be noted that an inflammatory response is a normal body process and for good reason. A certain level of inflammatory response is needed to protect the body from invading organisms, especially bacteria, viruses, and parasites. An acute inflammatory response is needed to activate the healing process for burns, mediated by a range of MMPs.

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In sprains or other ligament injuries, some inflammatory response is needed initially to initiate repair of the damage. In mechanical wounds, some inflammatory response is required for satisfactory wound healing and indeed anti-inflammatory drugs such as cortisone can impair healing when administered at the time of wounding. In fact, inflammation is too important to be dependent on a single pathway and so inflammation can be initiated by numerous different systems, and generally, if one fails or is thwarted, another can do some or all of the job.

Finally, it should be noted that it is not always clear what is and what is not an inflammatory disorder. A good example of this is insulin resistance, the underlying disorder in Type II Diabetes Mellitus and Metabolic Syndrome, and possibly a few other disorders as well. The inflammation hypothesis says that the enlarged fat cells drawn in macrophages, which excrete pro-inflammatory cytokines IL-6,  $\alpha$ -TNF, and IL1- $\beta$ , which via their receptors activate JNK to block IRS-1. There is significant evidence for this, but no standard anti-inflammatory agents are effective against insulin resistance. The competing lipid overload hypothesis says that the enlarged fat cells leak fatty acids, causing DAGS to accumulate in muscle cells, which inhibit insulin signaling through nPKCs and block IRS-1. At this time, there is no agreement on whether insulin resistance should be best understood as an inflammatory disorder.

II. Claims 13 and 14 also cover AIDS.

III. The claims also cover prevention. Thus, the claims cover preventing a person from getting AIDS, asthma.

(2) The nature of the invention and predictability in the art: The invention is directed toward the treatment of disease and is therefore physiological in nature. It is well

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established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: None is provided. The dosage information was apparently omitted from the specification.

(4) State of the Prior Art: These compounds are pyrazolyl adenine with a particular substitution pattern on the exocyclic N as well as elsewhere. So far as the examiner is aware, no pyrazolyl adenines of any kind have been used for the treatment of AIDS, ARDS, COPD, osteoporosis, etc.

(5) Working Examples: There are none to the treatment of any disease. There is testing to establish that these compounds are PDE-IV inhibitors, although no data is reported on any specific compounds.

(6) Skill of those in the art: One of ordinary skill in the art knows that there is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, histamine, fibrin, some PDE4 isoenzymes, kallikrein, plasmin, thrombin, PAF, Mac-1, VLA-4, VLA-5, VLA-6, VCAM-1, LFA-1, ICAM-1, Prostaglandins and cyclic endoperoxides (particularly prostacycline, prostaglandin E2, and thromboxane A2), leukotrienes (especially LTB4, LTC4, LTD4, and LTE4) and cytokines, and many, others. Examples of pro-inflammatory cytokines include IL-1-alpha, IL-1beta, IL-6, IL-8, IL-11, IL-12, IL-17, IL-18, GM-CSF, CNTF, OSM (Oncostatin M), MCP-1, CCL5 (RANTES), TGF-

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beta, ENA-78, Osteopontin, Cyclophilin A, LIF (leukemia inhibitory factor), leptin, MIP-1, TWEAK, MGSA, keratinocyte-derived chemokine, PF4, MCP-1 (GDCF), IFN-gamma, TNF- $\alpha$ , Absciscic acid, high mobility group box chromosomal protein 1 (HMGB-1), S100A12 (EN-RAGE), TRAIL, sCD40L, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-32, and IL-33. The Complement Pathway, which exists in two separate branches, uses C1, C4a, C4b, C2, C3a, C3b, C5a, C5b, C6, C7, C8 and C9, as well as the membrane attack complex (MAC) and other complexes, C3 and C5 convertase enzymes, PI3K-gamma, Magnesium ions, and Factors B, D, F, H, etc.

One of ordinary skill in the art also knows that mediation of inflammation is among the most pervasive and complex of all body process. There are very complex interactions among just the cytokines. As a second example, the Hageman factor is a protein that initiates three different processes: a) the intrinsic clotting process which operates via thrombin and fibrin, b) the fibrinolytic system which produces fibrinolysis via plasmin and 3) the kallikrein/kinin cascade, which produces the kinins, e.g. bradykinin. Further, Plasmin can also activate C3 and C5 in the complement cascade (an entirely separate set of vascular events) producing C3a and C5a, respectively, as can thrombin.

One of ordinary skill in the art also knows that there are many paradoxical features in the inflammation system. As an example, in lung inflammation, nitric oxide appears to be a pro-inflammatory mediator in acute situations e.g. ARDS but anti-inflammatory in more stable situations. As a second example, the cytokine TGF-beta-1 possesses both pro-inflammatory and anti-inflammatory activities. Virtually all cells have TGF-beta-1 receptors, and the cytokine has many other roles other than in inflammation. As a third example, CRF appears to have both pro-inflammatory and anti-inflammatory activities.

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And in fact, there is a tremendous diversity in the combination of mechanisms that produce inflammation. For example, Atherosclerosis arises from the accumulation of macrophage white blood cells and is promoted by low density (especially small particle) lipoproteins. Very few, if any, other inflammatory disorders have this particular mechanism.

Thus, one of ordinary skill in the art knows that, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

For a compound or genus to be effective against inflammation generally is contrary to the present understanding of medical science. Thus, it is not reasonable for any agent to be able to treat inflammation generally. That is, the skill is so low that no compound effective generally against inflammatory disorders has ever been found. In terms of the individual inflammatory disorders, this is completely varied.

There is no pharmaceutical treatment for COPD per se; no pharmaceutical intervention will slow the progression of the disease. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself. Asbestosis, perhaps the most important of the most Occupational Lung Diseases, has no pharmacological treatment. What treatment there is, is palliative, notably Oxygen therapy to relieve the shortness of breath, respiratory physiotherapy to remove secretions from the lungs by postural drainage, chest percussion, and vibration, and nebulized medications to thin

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secretions, but these of course do not treat the disorder itself. There is also no pharmacological treatment of ARDS, only for its symptoms, such as pulmonary arterial hypertension, and management of infection with e.g. antibiotics.

With regard to AIDS, the only drugs found effective against AIDS are those which interfere with the lifecycle of the HIV virus itself. There is no reason to think that these compounds have such a property.

With regard to prevention, the skill level is essentially nil in many types of inflammatory disorders. For example, Cystic fibrosis, ARDS, Gouty arthritis, Rheumatoid arthritis, Ankylosing spondylitis, Conjunctivitis, Psoriasis, Osteoarthritis, Asthma, COPD, and Eczema and just some of the inflammatory disorders which are known to be not preventable by pharmaceutical means. There are of course many drugs to treat e.g. asthma, but these do not prevent a person from having asthma in the first place.

(7) The quantity of experimentation needed: Owing to the factors listed above, especially in points 1, 3, 4 and (6), experimentation needed will be extensive. Because of the sheer scope of this claim language, dozens of unrelated diseases will have to be tested. Many of these are already known to be resistant to pharmacological treatment as noted above.

As of the time of filing, and indeed as of the present, no PDE-4 inhibitor of any kind has been approved by the FDA for the treatment of any disorder. The examiner notes that extensive efforts have been made to try to get Ariflo® (cilomilast) and Daxas® (roflumilast) to be effective against COPD (and asthma) without success, evidence of the low skill level in this art. It is not known, of course, whether these claimed compounds affect the same isoenzymes as cilomilast and roflumilast.

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MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

### ***Specification***

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

In addition, the abstract is objected to as failing to set forth what the invented compounds actually look like.

### ***Information Disclosure Statement***

The information disclosure statement filed 03/04/2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the Foreign Patents referred to therein has not been considered, because these were not provided.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/  
Primary Examiner  
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11/30/2009